

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2005/001451

International filing date (day/month/year)
15.04.2005

Priority date (day/month/year)
15.04.2004

International Patent Classification (IPC) or both national classification and IPC
A61K38/17, A61K39/395, A61P7/02

Applicant
ATHERA BIOTECHNOLOGIES AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/001451

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/001451

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 4,5,10,11

because:

☒ the said international application, or the said claims Nos. 4,5,10,11 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/001451

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------------|
| Novelty (N) | Yes: Claims | 5,9,11 |
| | No: Claims | 1-4,6-8,10 |
| Inventive step (IS) | Yes: Claims | - |
| | No: Claims | 1-11 |
| Industrial applicability (IA) | Yes: Claims | 1-3,6-9 |
| | No: Claims | - |

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 4,5,10,11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited documents

Reference is made to the following documents:

- D1: US 2003/152513 A1 (BLANKENBERG FRANCIS G ET AL) 14 August 2003
- D2: WO 02/067857 A (SURROMED, INC) 6 September 2002
- D3: MARI C ET AL: "Annexin V, a new therapeutic tool in atherosclerosis" JOURNAL OF NUCLEAR MEDICINE, vol. 43, no. 5 Supplement, May 2002, page 7P, XP009051427 & 49TH ANNUAL MEETING OF THE SOCIETY OF NUCLEAR MEDICINE; LOS ANGELES, CA, USA; JUNE 15-19, 2002
- D4: THIAGARAJAN PERUMAL ET AL: "Inhibition of arterial thrombosis by recombinant annexin V in a rabbit carotid artery injury model" CIRCULATION, [Online] vol. 96, no. 7, 1997, pages 2339-2347, XP002338645
- D5: US 2003/170241 A1 (AUKRUST PAL ET AL) 11 September 2003
- D6: SHERER Y ET AL: "Immunomodulation for treatment and prevention of atherosclerosis" AUTOIMMUNITY REVIEWS 2002 NETHERLANDS, vol. 1, no. 1-2, 2002, pages 21-27, XP002338646
- D7: ALVES J D ET AL: "Atherosclerosis, oxidative stress and auto-antibodies in systemic lupus erythematosus and primary antiphospholipid syndrome" IMMUNOBIOLOGY, FISCHER, STUTTGART, DE, vol. 207, no. 1, 2003, pages 23-28, XP004954257
- D8: GOLDENBERG H B ET AL: "Human antibody to phosphorylcholine is bactericidal against Haemophilus influenzae." ABSTRACTS OF THE GENERAL MEETING OF

THE AMERICAN SOCIETY FOR MICROBIOLOGY; vol. 103, 2003, pages D-116,
XP009051386 & 103RD AMERICAN SOCIETY FOR MICROBIOLOGY GENERAL
MEETING; WASHINGTON, DC, USA; MAY 18-22, 2003

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

Novelty and inventive step

Claims 1-5 (Annexin V for preventing atherothrombosis and/or plaque rupture)

Subject-matter of claims 1-4 is considered to lack novelty under Art. 33(1) and (2) PCT as being anticipated by D1, D2, and D4. D1 disclose the use of annexin V for detecting and treating vulnerable (instable) plaque. D2 teaches the use of modified annexin V for treating a subject at risk of thrombosis, preferably coronary thrombosis or arterial thrombosis. D4 teaches inhibition of arterial thrombosis by annexin V in a rabbit carotid artery injury model. The above disclosure of D1, D2 and D4 anticipates novelty of claims 1-4.

Present claims 1-5 are considered to lack an inventive step under Art. 33(1) and (3) PCT. In case novelty of claims 1-4 over D1, D2 and D4 is acknowledged, the claims would be considered to be obvious based on those documents. Moreover, D3 proposes annexin V as a suitable plaque stabilizes in vivo. The choice of systemic lupus erythematosus (SLE) patients (claim 5) cannot render the claimed subject matter inventive as atherosclerosis and coronary artery disease are known in the prior art as the major SLE complications - see D7.

Claims 6,7,9 (purified subfraction of pooled immunoglobulins)

Novelty of claims 6 and 7 is anticipated by D8 disclosing human antibodies to phosphorylcholine (ChoP) isolated by affinity purification for total gamma globulin fraction of pooled human sera by passage over a p-aminophenyl ChoP-bead column. D8 is silent about the ability of ChoP-specific antibody to inhibit antibodies binding to Annexin V and/or to promote binding of Annexin V to endothelium. However, it follows from the specification that the subfraction according to the present invention may be obtained by affinity

purification based on binding to a phosphocholine conjugate. Consequently, subfraction of D8 obtained by such an affinity purification is considered to fall within the scope of present claims 6 and 7. D8 fails to disclose any medical use of the disclosed subfraction, consequently claim 9 is new. However such use is considered to be obvious based on the bactericidal activity of the subfraction disclosed in D8. Claim 9 thus cannot be considered to involve an inventive step.

Claims 8,10,11 (pooled immunoglobulins or purified subfraction thereof for preventing atherothrombosis and/or plaque rupture)

Claims 8 and 10 are considered to lack novelty over the disclosure of D5 and D6. D5 discloses use of intravenous immunoglobulin (Ivlg) for the treatment of non-viral and non-autoimmune induced heart disorders including coronary syndromes caused by a rupture of an atherosclerotic plaque in one of coronary arteries. D6 discloses immunomodulation including administration of Ivlg for treatment and prevention of atherosclerosis. Ivlg was found to be effective both during fatty streak and plaque formation of atherosclerosis.

Claim 11 appears to be new but could not be considered inventive as being obvious in view of at least combination of D6 and D8 for the reasons stated above for claim 5.

Industrial applicability

Subject-matter of claims 1-3, 6-9 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

For the assessment of the present claims 4,5,10,11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application (clarity)

Claims 6,7 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Those claims are directed to a purified subfraction of pooled immunoglobulins defined by the desirable function thereof, namely the ability thereof to inhibit antibodies binding to annexin V (claim 6) or to promote binding of annexin V to endothelium (claim 7). Moreover, the agent itself is defined by the way of preparation thereof - as a subfraction purified for pooled immunoglobulins, without any structural definition, rendering the subject-matter further unclear. Due to the combination of functional definition by a result to be achieved and product-by process definition, the claims lack clarity under Article 6 PCT and support under Article 5 EPC to such an extent that no complete search of the subject-matter claimed was possible. Consequently, the search has been performed for the only embodiment supported by the description, namely the subfraction prepared by affinity purification based on binding to a phosphorylcholine conjugate - see page 7, lines 19-23.